NIAID Media Roundtable

On the Frontlines of Influenza Research

Anthony S. Fauci, M.D.

National Institute of Allergy and Infectious Diseases

National Institutes of Health

Bethesda, Maryland, USA

November 15, 2004

On the Frontlines of Influenza Research

NIAID Participants

Anthony S. Fauci, M.D., Director, NIAID

Cristina Cassetti, Ph.D., Program Officer, Influenza, SARS, and Related Viral Respiratory Diseases Section, Division of Microbiology and Infectious Diseases

Maria Giovanni, Ph.D., Assistant Director for Microbial Genomics and Advanced Technology, Division of Microbiology and Infectious Diseases

Linda Lambert, Ph.D., Acting Chief, Influenza, SARS, and Related Viral Respiratory Diseases Section, Division of Microbiology and Infectious Diseases

Brian Murphy, M.D., Co-Chief, Laboratory of Infectious Diseases

Kanta Subbarao, M.D., Senior Investigator, Respiratory Viruses Section, Laboratory of Infectious Diseases

The Burden of Influenza

- 250,000 to 500,000 deaths globally/yr.
- 36,000 deaths and >200,000 hospitalizations/yr. in U.S.
- $37.5 billion in economic costs/yr. in U.S. related to influenza and pneumonia.
- Ever-present threat of pandemic influenza.

Sources: CDC, WHO, Am. Lung. Assoc.

Effectiveness of Influenza Vaccine

- 70-90% in healthy adults <65
- 60% in adults ≥65
- Substantial reductions in direct medical costs and indirect medical costs due to absenteeism

State and Territorial Epidemiologists Reports

State health departments report the estimated level of influenza activity in their states each week:

No Activity: No laboratory-confirmed cases of influenza and no reported increase in the number of cases of ILI.

Sporadic: Small numbers of laboratory-confirmed influenza cases or a single influenza outbreak has been reported, but there is no increase in cases of ILI.

Local: Outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in a single region of the state.

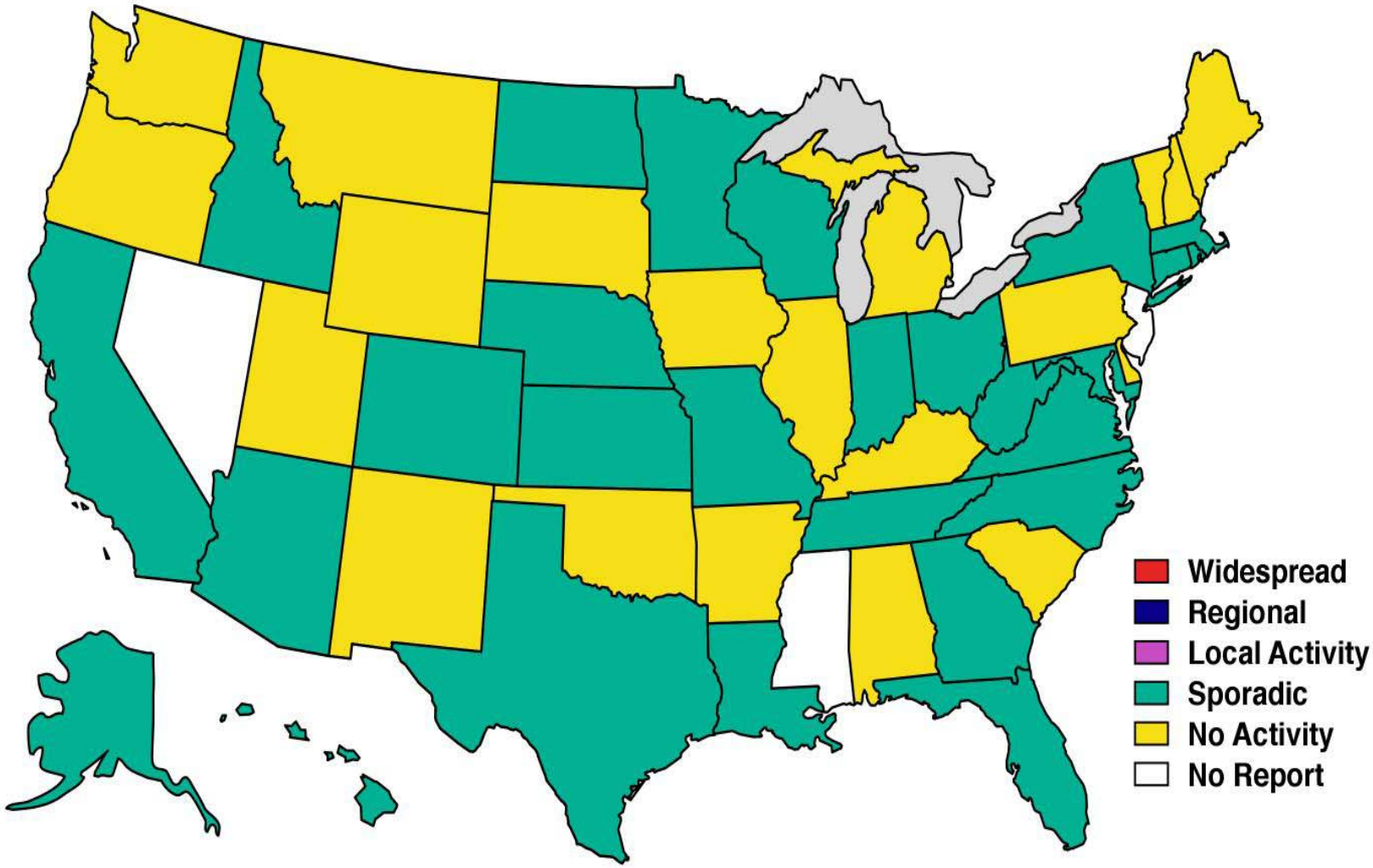
Regional: Outbreaks of influenza or increases in ILI and recent laboratory confirmed influenza in at least 2 but less than half the regions of the state.

Widespread: Outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in at least half the regions of the state.

Source: CDC

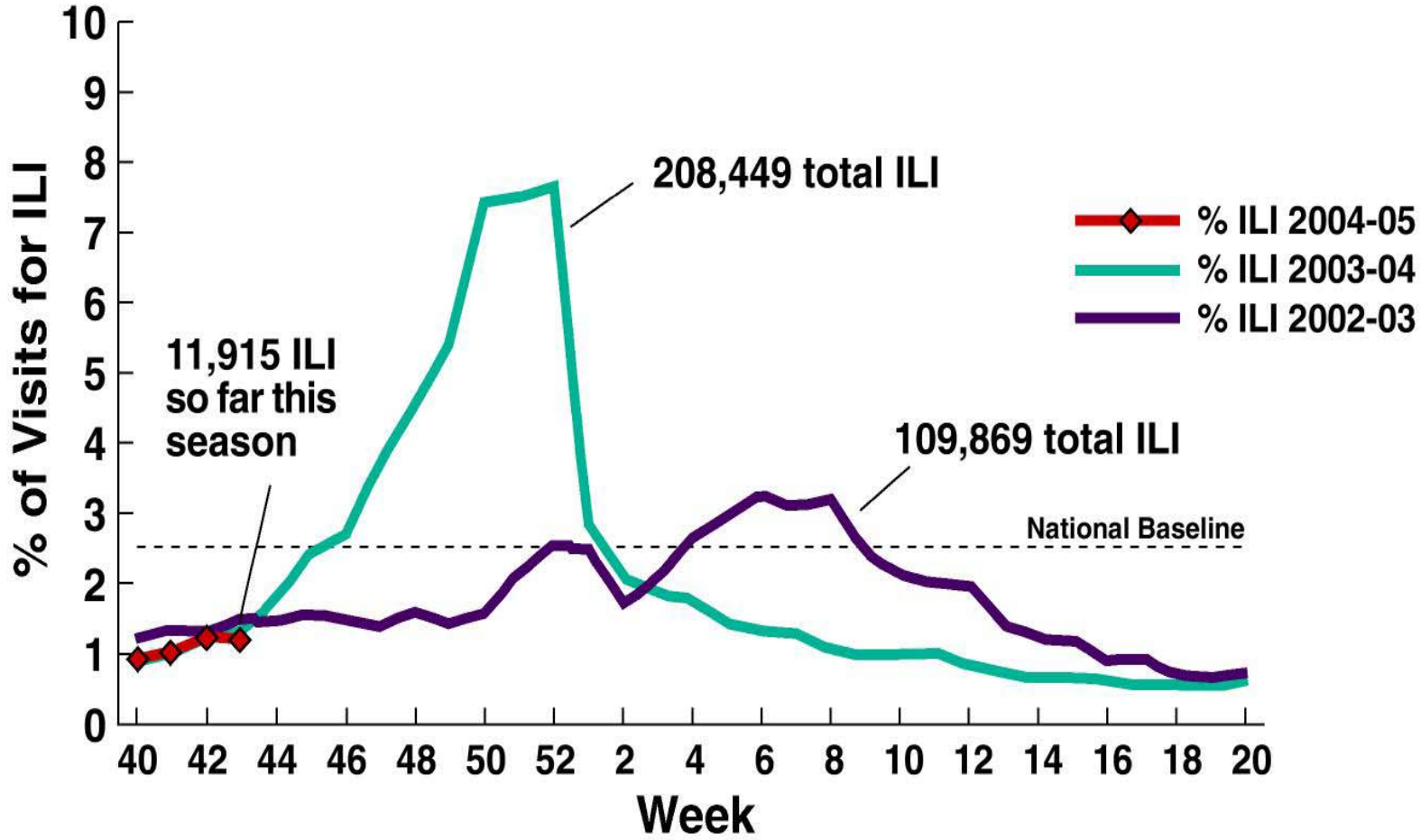
Weekly Influenza Activity Estimates Reported by State and Territorial Epidemiologists

Week Ending November 6, 2004 - Week 44



Source: CDC

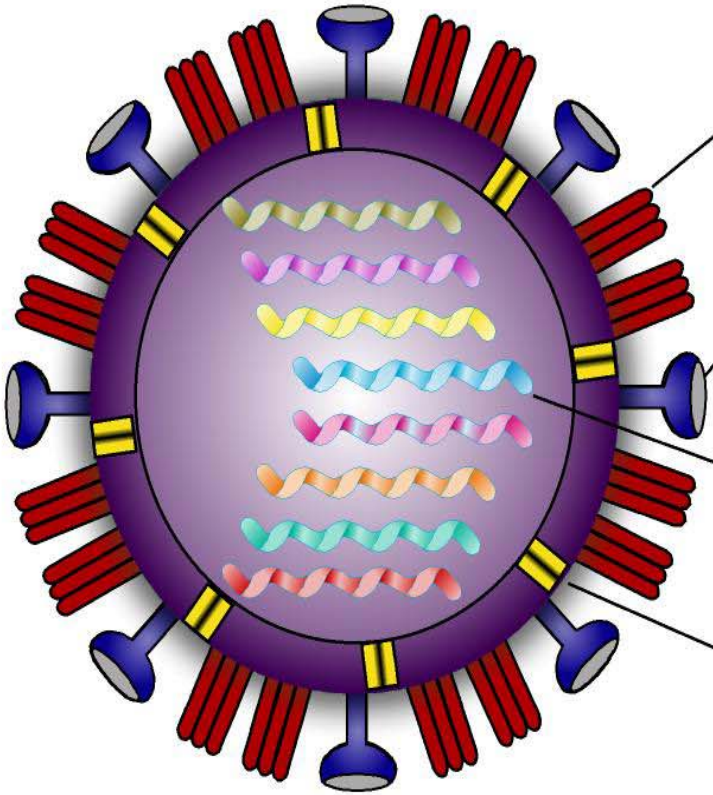
Percent of Visits for Influenza-Like Illness Reported by Sentinel Providers, National Summary 2004-05 and Previous 2 Seasons



The 2002-03 and 2003-04 seasons were selected for comparison because they were the most recent A(H3N2) seasons of mild and moderate severity, respectively.

Source: CDC

Influenza A Virus



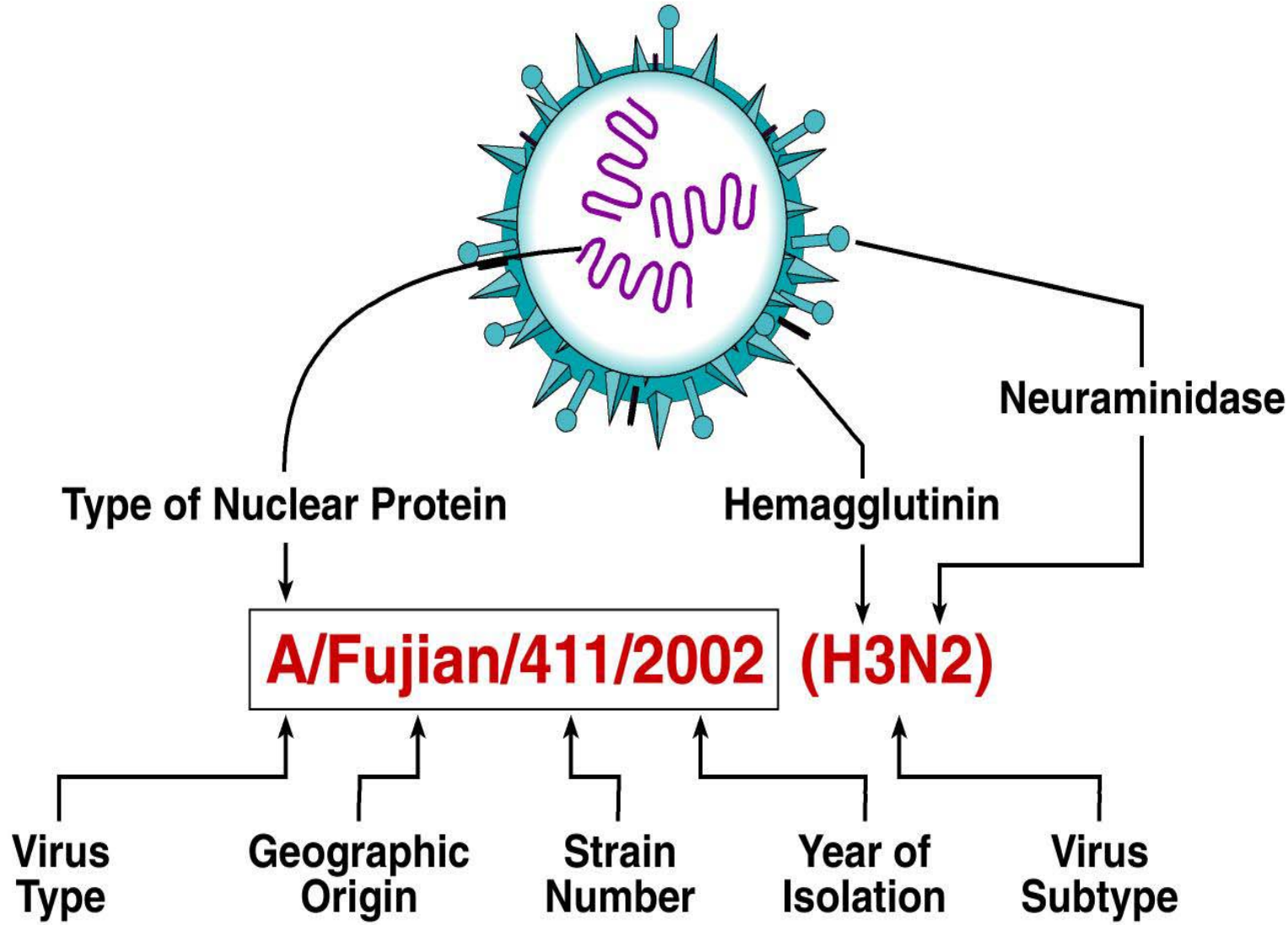
Hemagglutinin (H) - 15 subtypes
(attachment, penetration)

Neuraminidase (N) - 9 subtypes
(release)

8 viral genes
(assembly, replication, etc.)

M2 Protein
(penetration)

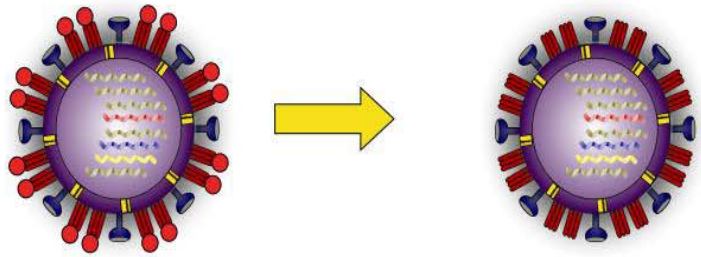
Influenza Virus Nomenclature



Source: Subbarao/Murphy

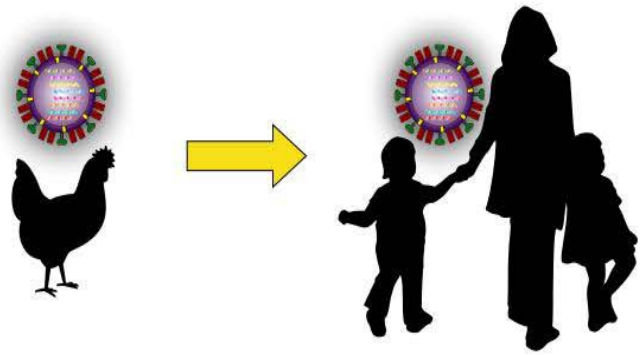
Emergence of New Human Influenza Subtypes

Drift (minor mutations)

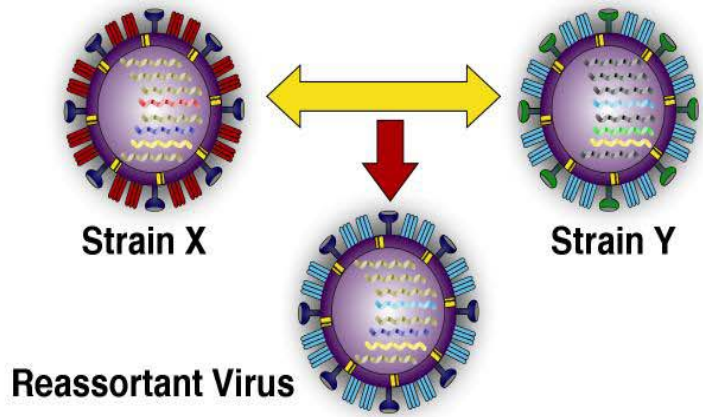


Shift (major change)

Jumping Species



Reassortment



Past Antigenic Shifts

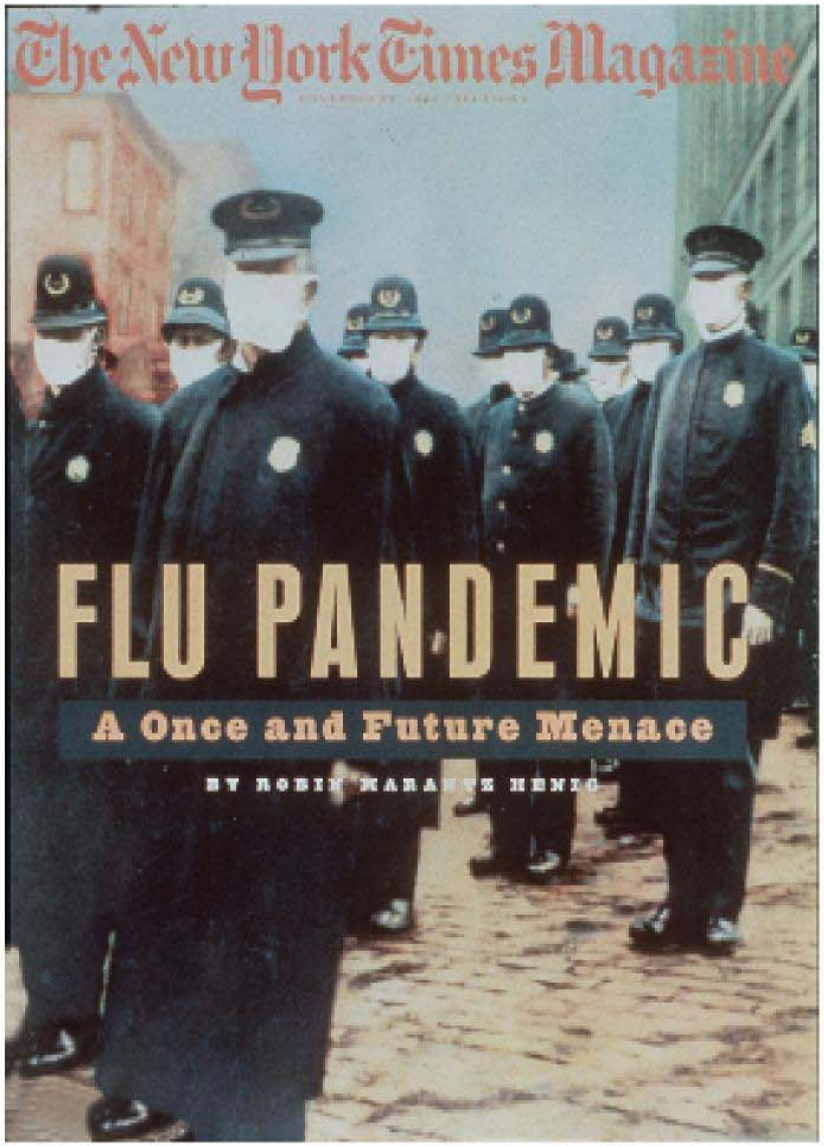
1918	H1N1	Spanish Influenza	20-40 million deaths
1957	H2N2	Asian Flu	1-2 million deaths
1968	H3N2	Hong Kong Flu	700,000 deaths
1976	H1N1	Swine Flu	No pandemic
1997	H5N1	Bird Flu	Pandemic averted?

Definition of a Pandemic Influenza A Virus

- Isolation from humans of an influenza A virus with a novel hemagglutinin or a novel hemagglutinin and neuraminidase gene.
- Susceptibility (lack of antibody) to this novel virus, in a large proportion of the population.
- Demonstrated ability of the virus to cause disease and spread from person-to-person.

Source: Subbarao/Murphy

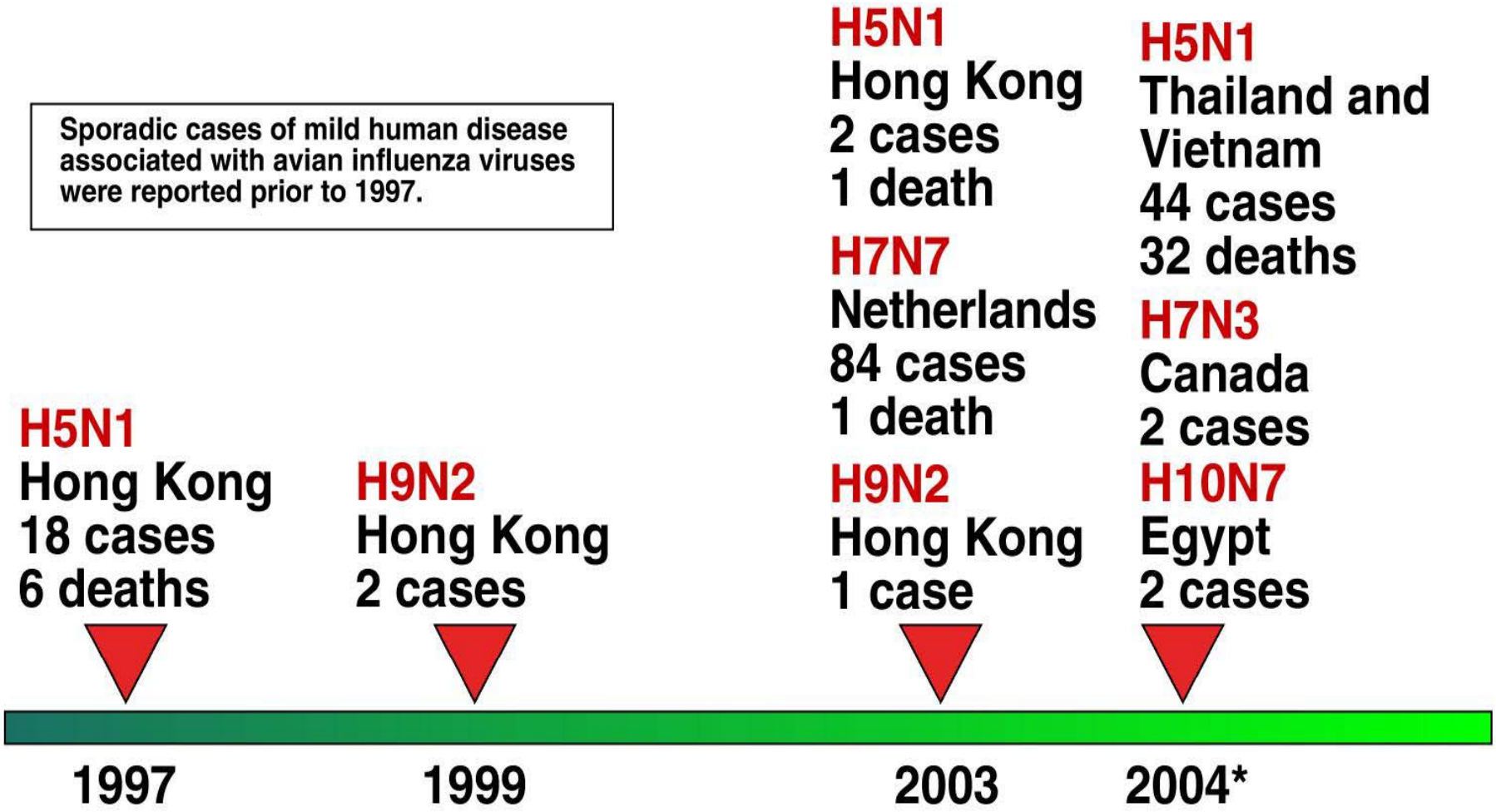
The Influenza Pandemic of 1918-1919



- 500 million people infected worldwide
- 20-40 million deaths worldwide; ~50 percent in people ages 20-40
- >500,000 deaths in United States; 196,000 in October, 1918 alone

Documented Human Infection with Avian Influenza Viruses: A Timeline

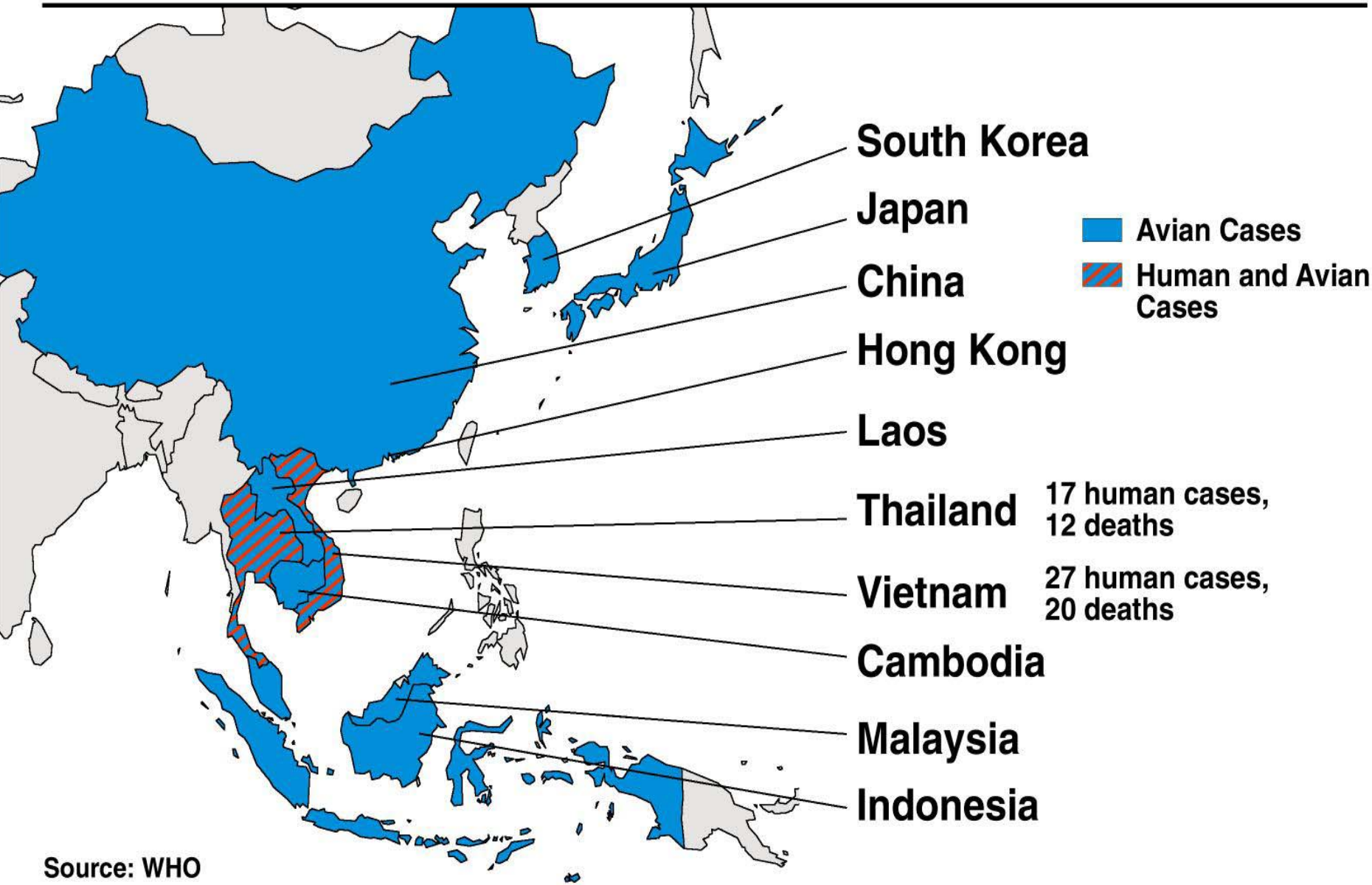
Sporadic cases of mild human disease associated with avian influenza viruses were reported prior to 1997.



Source: WHO, PROMED

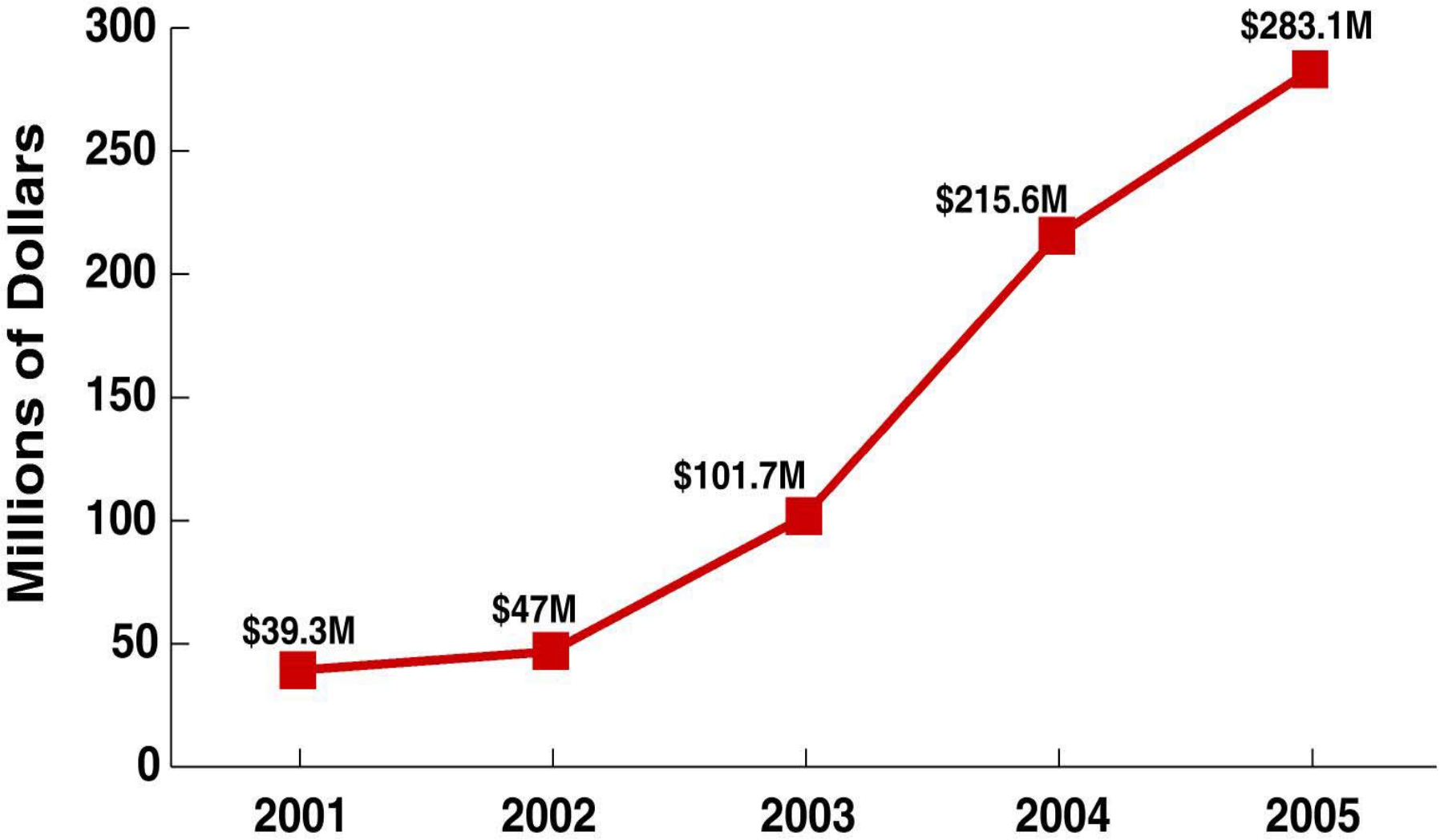
*Through 25 October

H5N1 Influenza in Asia, 2004

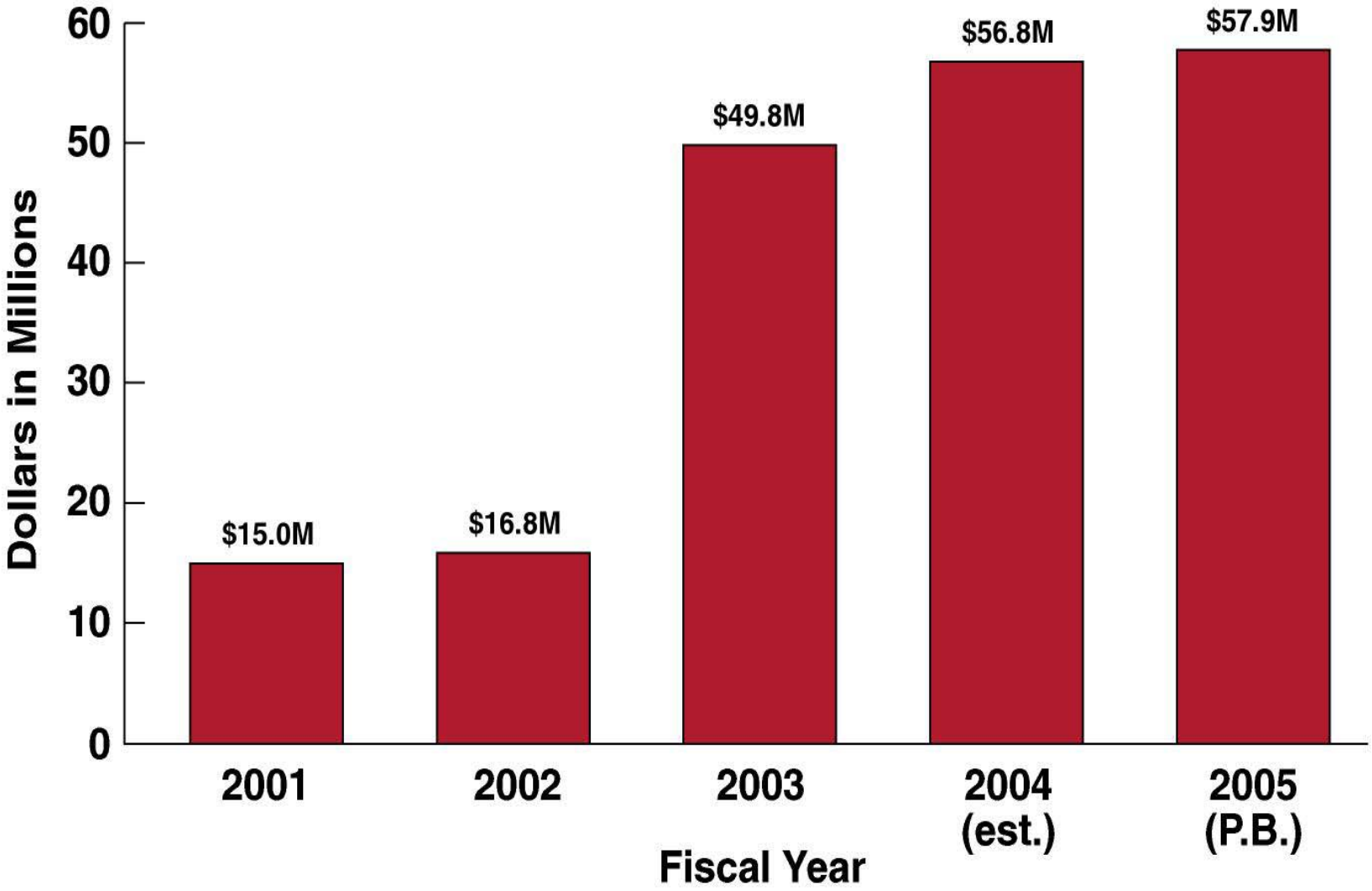


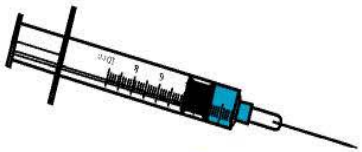
Source: WHO

HHS Influenza-Related Funding



NIAID Influenza Research Funding



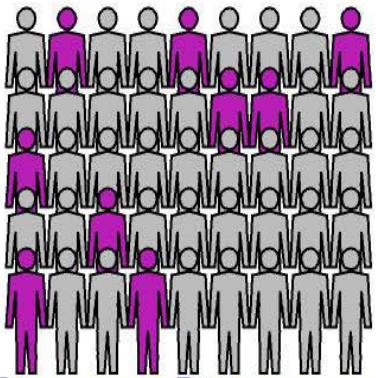


Vaccines

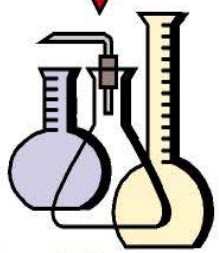
Therapeutics

Diagnostics

NIAID Influenza Research



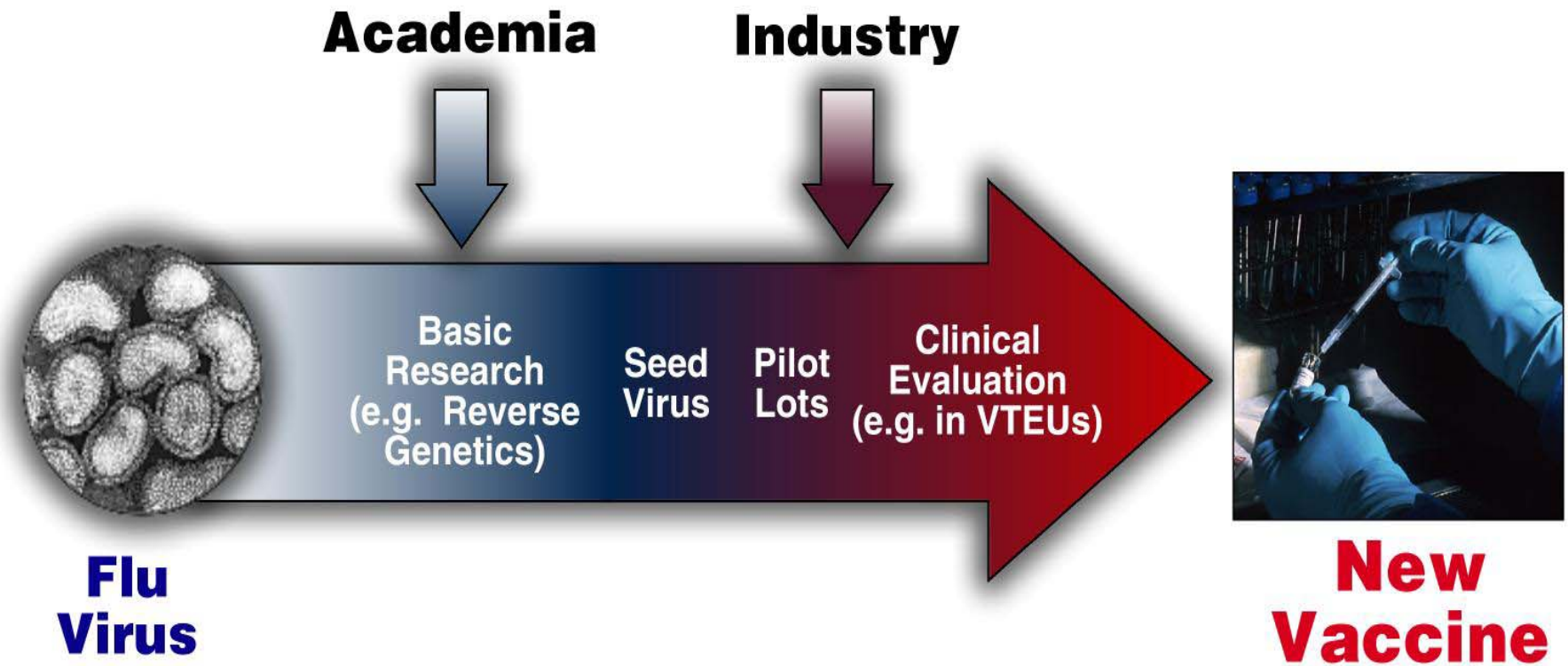
Surveillance and Epidemiology



Basic Research

Expansion of Research Capacity

NIAID Role in Influenza Vaccine Development



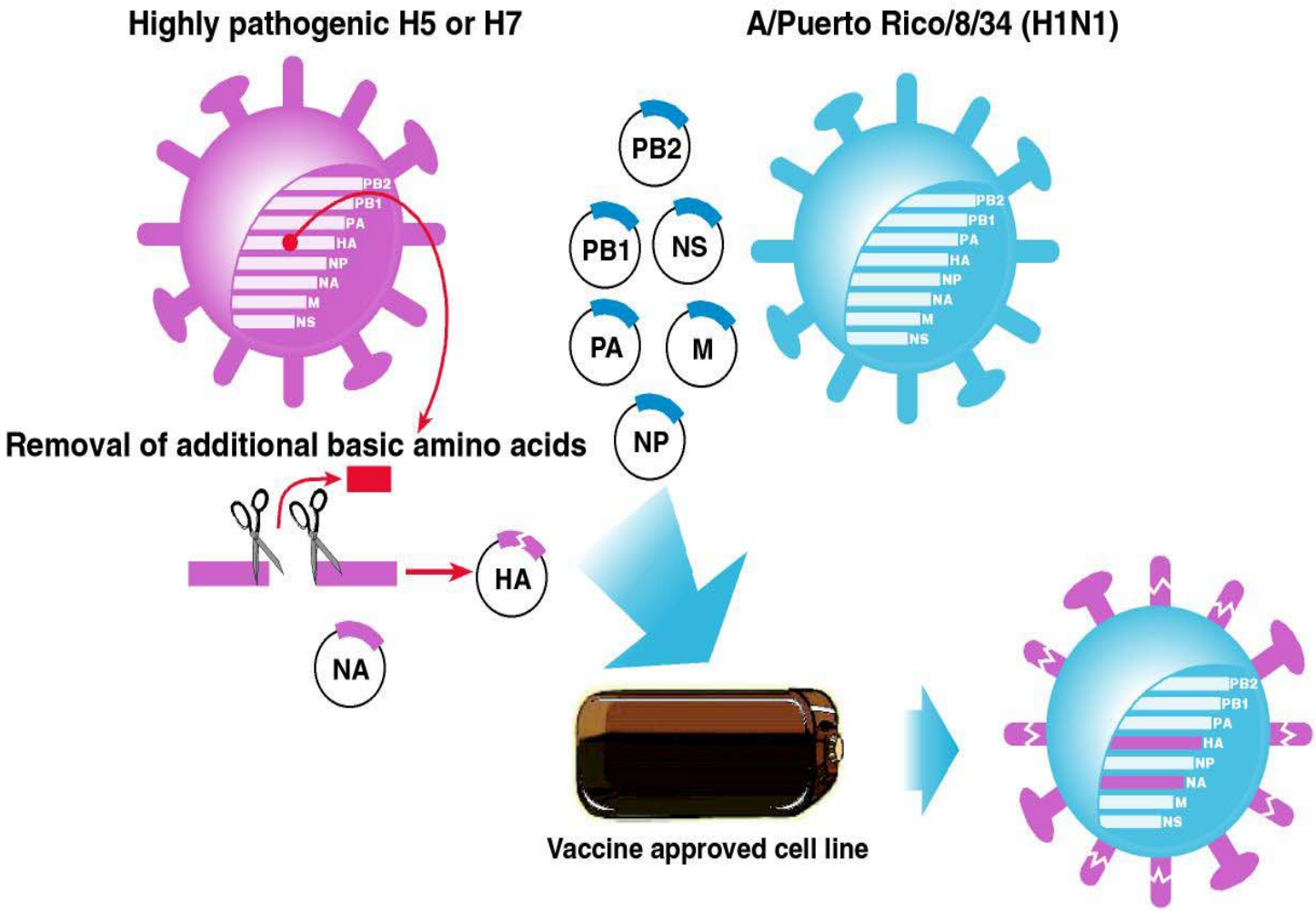
NIAID-Supported Influenza Research Activities
Basic Research

- Understand the mechanism of pathogenicity of pandemic influenza viruses; identify markers that signal the emergence of influenza strains with increased virulence
- Understand how new influenza viruses emerge from animal reservoir to cause a pandemic
- Study replication efficiency and transmissibility of H5N1 influenza viruses in different animal species
- Develop animal models to study pandemic influenza viruses

NIAID-Supported Research on 1918 Pandemic H1N1 Influenza Virus: Current Studies

- Complete sequence of 1918 influenza virus genes
- Identify signature sequences responsible for virulence
- Determine molecular mechanisms leading to emergence
- Understand contribution of 1918 HA and NA genes to unprecedented virulence

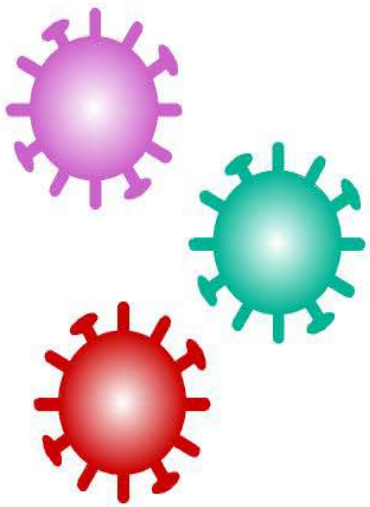
Influenza Seed Virus for Inactivated Virus Vaccine Production Using a Reverse Genetics System



Source: Webster et al: *Vaccine* 20:3165 (2002); Science 302:1519 (2003)

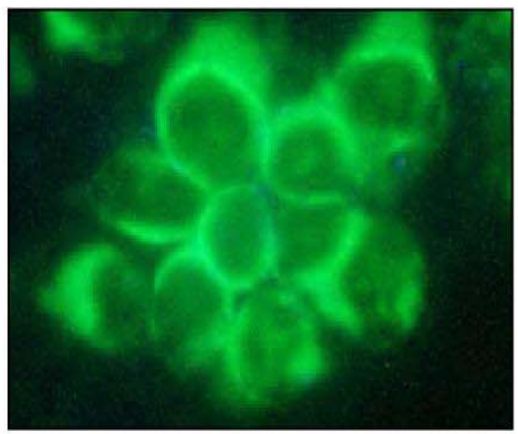
Influenza Vaccine Production: Cell Culture as an Alternative to Chicken Eggs

Identify target flu strains

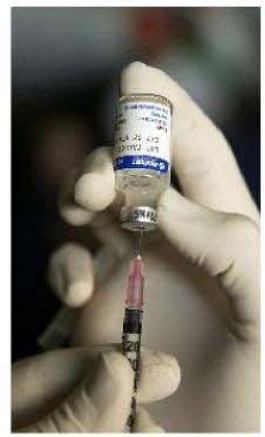


Provide target viruses to vaccine manufacturers

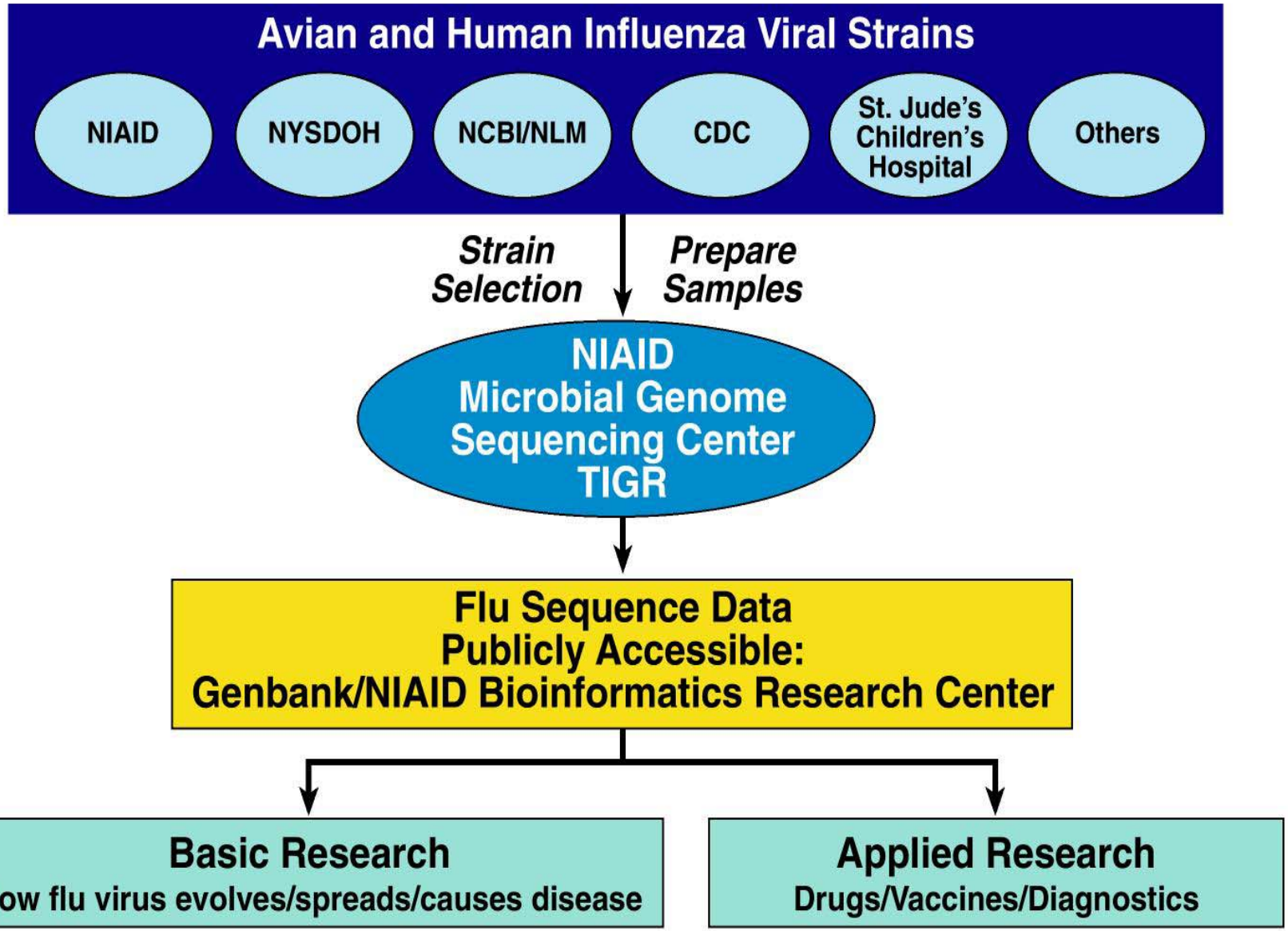
Egg-based



Cell culture-based



NIAID Influenza Genome Project



NIAID-Supported Influenza Research Activities

Product Development: Diagnostics and Therapeutics

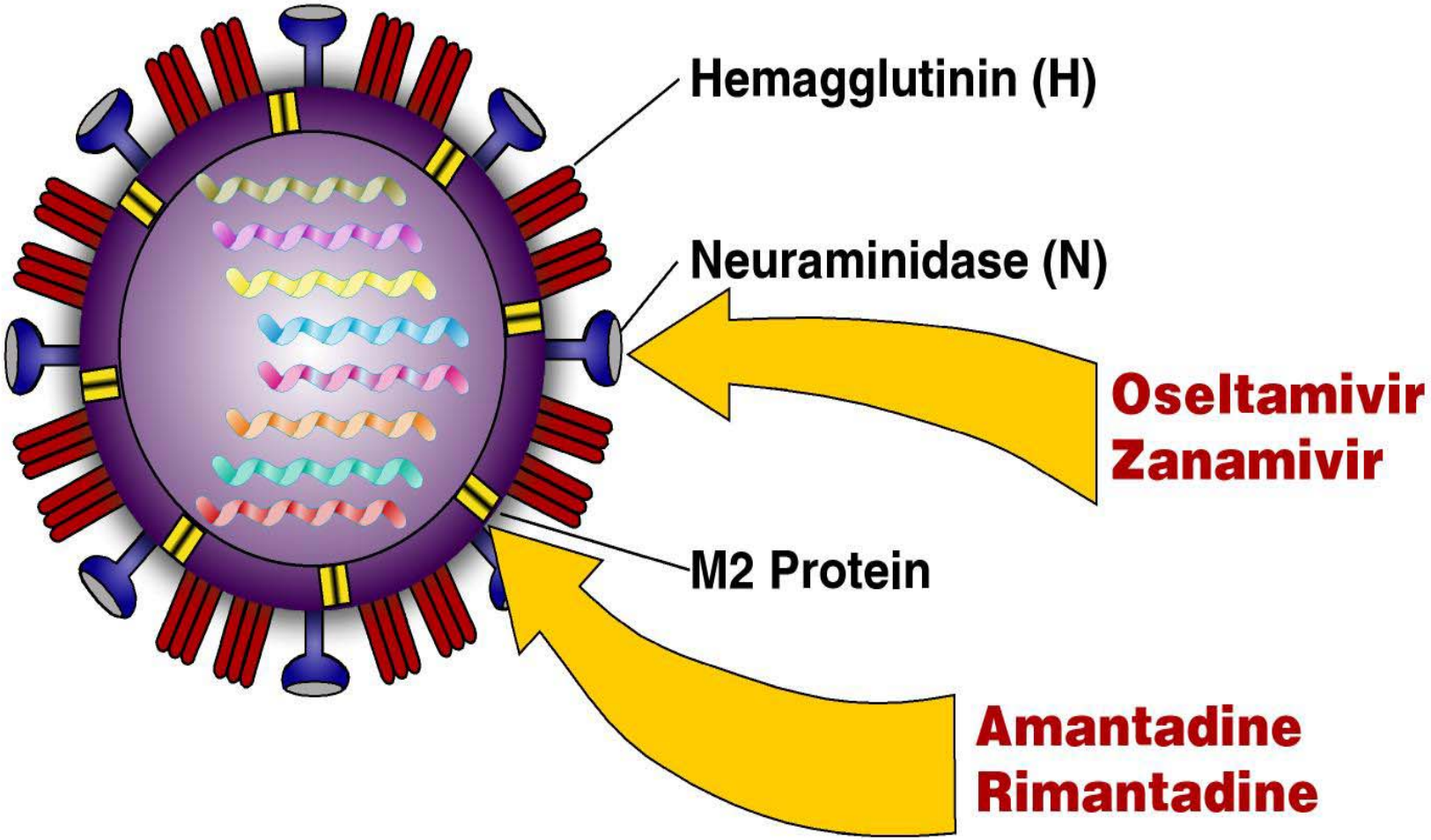
Diagnostics:

- Rapid, sensitive, and portable diagnostic devices to detect influenza virus, determine type, and differentiate from pathogens that cause influenza-like illness

Therapeutics:

- Development of novel influenza anti-viral drugs (e.g. long-acting neuraminidase inhibitors and siRNAs)

Antiviral Therapies for Influenza

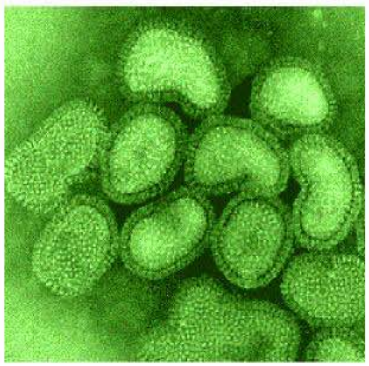


NIAID-Supported Influenza Research Activities
Product Development: Vaccines

- Generate vaccine reference strains (reverse genetics)
- Manufacture vaccine pilot lots and execute clinical trials
- Advance cell culture-based technology
- Investigate protective role of herd immunity
- Develop novel influenza vaccines that do not require annual update
- Evaluate strategies to extend vaccine supplies

Influenza Vaccine Production Timeline

Jan – May | Jun - Jul | Aug | Sep | Oct - Nov



Virus Selection

- FDA advisory panel selects 3 strains
- CDC provides new strains of the seed virus to the FDA
- FDA distributes the 3 seed viruses to manufacturers

Production Begins

FDA Testing, Licensure

Filling/ Packaging

- Vaccine is filled into vials and syringes; packaged for distribution

Product Release/ Shipping

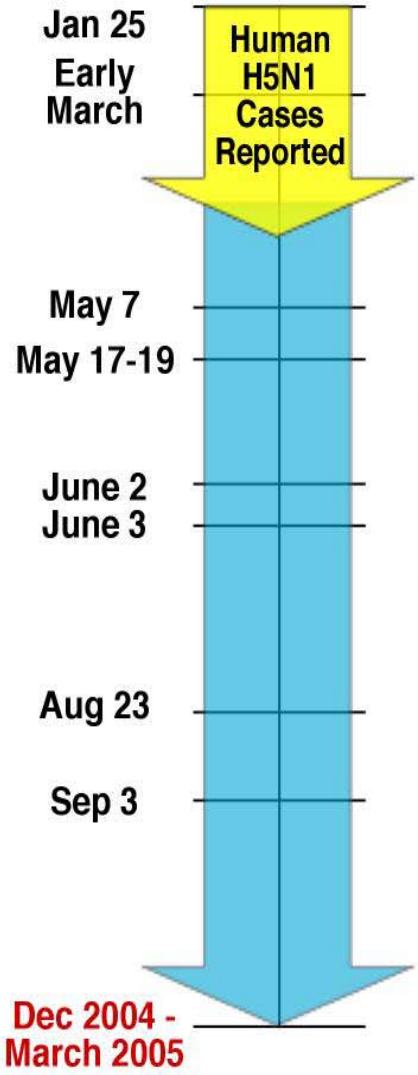
Vaccination Begins

- Immunity develops approximately 2 weeks after vaccination

2004-2005 Trivalent Influenza Vaccine: A/H3N2 (Fujian), A/H1N1 (New Caledonia), B (Shanghai)

- Conventional inactivated vaccine
- Live attenuated cold-adapted (ca) vaccine

NIAID H5N1 Vaccine Production - 2004



Jan 25 — St. Jude receives reference virus (A/VN/1203/04) from Hong Kong University

Early March — St. Jude produces H5N1 vaccine candidate using reverse genetics

May 7 — USDA select agent exemption of reference virus

May 17-19 — NIAID awards H5N1 letter contracts for H5N1 vaccine production to Aventis and Chiron

June 2 — Reference virus sent to NIAID

June 3 — Reference virus sent to Aventis; production of master seed and working seed begins immediately

Aug 23 — Reference virus sent to Chiron; production of master seed and working seed begins immediately

Sep 3 — Pre-IND teleconference with FDA; guidance provided regarding NIAID manufacturing and development plan

Dec 2004 - March 2005 — Estimated date for delivery of vaccine by Aventis and Chiron

NIAID to initiate clinical trials in VTEUs within 30 days of receipt of each vaccine

NIH NEWS RELEASE

National Institutes of Health

National Institute of Allergy and Infectious Diseases

FOR IMMEDIATE RELEASE
Thusday, May 27, 2004

NIAID Announces Contracts to Develop Vaccine Against H5N1 Avian Influenza

NIH NEWS RELEASE

National Institutes of Health

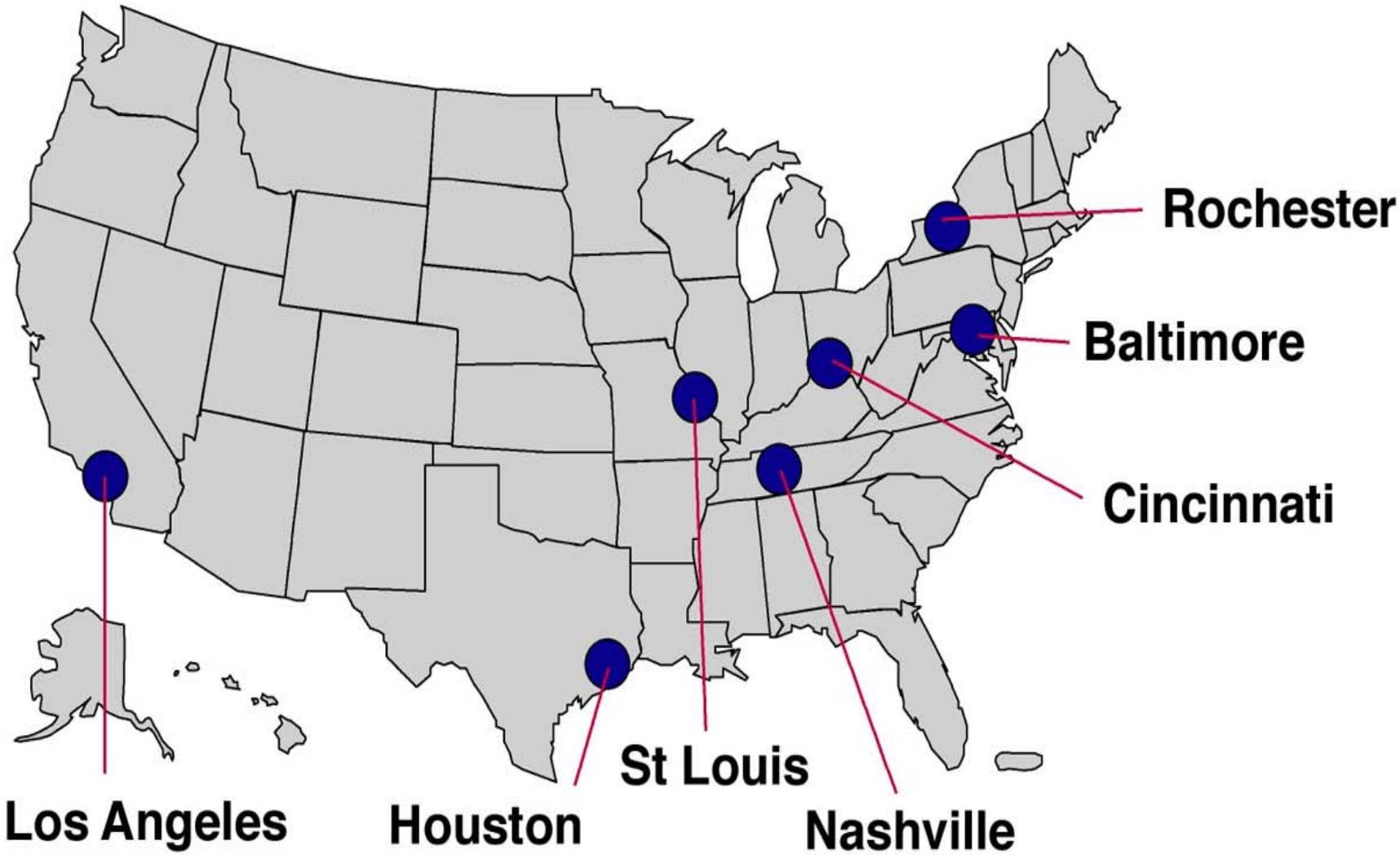
National Institute of Allergy and Infectious Diseases

FOR IMMEDIATE RELEASE
Tuesday, August 17, 2004

NIAID Taps Chiron to Develop Vaccine Against H9N2 Avian Influenza

Award Part of NIAID Pandemic Influenza Preparedness Program

NIAID's Network of Vaccine and Treatment Evaluation Units (VTEUs)



Associated Press

October 5, 2004

U.S. Flu Vaccine Supply Halved

Health Officials Face Record Shortage as Britain Shuts Down Supplier

Americans' supply of flu vaccine was cut in half Tuesday as Britain abruptly shut down a major supplier just as flu season is about to begin. Facing a record shortage, U.S. health officials scrambled to reserve remaining shots for the elderly and others at highest risk from influenza.

Addressing the Fragile Vaccine Enterprise

- Research resources: developing and sharing new technologies, e.g.
  - reverse genetics
  - cell culture-based vaccines
  - recombinant DNA technologies
  - "perennial" vaccines based on conserved epitopes

Addressing the Fragile Vaccine Enterprise (continued)

- Incentives to industry, e.g.
  - regulatory relief
  - guaranteed purchases and fair pricing
  - liability protection
  - research resources and clinical trials capacity
  - tax incentives

The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

VOLUME 351 NOVEMBER 3, 2004 NUMBER 19

Invited Commentary:

Intradermal Influenza Vaccination: Can Less Be More?

John R. La Montagne and Anthony S. Fauci

"These studies raise the possibility of using alternative routes of immunization (e.g., intradermal as opposed to intramuscular, administration) with smaller doses of vaccine as a means of "stretching" available doses of influenza vaccine in times of shortages."

NIAID

SEARCH

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
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Focus on the Flu

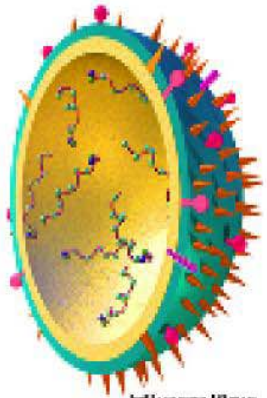
The National Institute of Allergy and Infectious Diseases (NIAID) supports investigators working on the front lines of the battle against flu. Follow the links below to learn about the latest in drug development, vaccine technologies, and efforts to prevent flu outbreaks. You can also learn facts about the flu, find out how to tell the difference between a cold and the flu, and get more information about the flu from other organizations.

What Should I Know About the Flu?

- Flu Fact Sheet - General information on prevention, diagnosis, and treatment of the flu
- Flu Drugs Fact Sheet - Information on drugs used to prevent and treat the flu.
- Is It a Cold or the Flu? (PDF)
- ¿Es un Resfrío o la Influenza? (PDF)
- What to Do About the Flu

http://www.niaid.nih.gov/newsroom/FocusOn/Flu04

- Treating the Flu
  - Fighting Back: New Drugs Against Flu
  - For a Brighter Flu Picture, Change the Channel
- Preventing the Flu
  - Scrambling for an Egg Alternative
  - One Shot Fits All?
  - Reverse Genetics
  - Taking Aim
  - A Nasal Spray Flu Vaccine
  - Half-Dose Influenza Vaccine Study
- Pandemic Preparedness
  - NIAID Lab Helps Ready Us for Potential Pandemic
  - "Hidden" Protein May Explain Why Some Flus Are More Dangerous Than Others
  - Surveillance Experts Find New Route for Avian Flu
  - Toxic Traces: What Made the 1918 Influenza Virus So Deadly?
  - First U.S. Clinical Trials of Bird Flu Vaccine Begin
  - "Development of a Clinical Trial Plan for Pandemic Influenza Vaccines" Workshop



Influenza Virus